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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,875	09/16/2003	Shi-Lung Lin	89188.0050	3099

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
10/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/663,875	LIN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/26/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,19 and 58-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,19 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 06/10/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/11/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 06/10/2008, claims 1-8, 11, 19 and 58-60 are pending and currently under examination in the application.

Response to Applicant's arguments is moot as the previous rejections of record have been withdrawn.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 58-60 are drawn to the isolated RNA of claim 1 wherein the artificial intron contains sequence that targets an exon of the target gene.

Applicant points to page 17 of the specification for support which discloses antisense compounds targeted to a region of the integrin B1 gene that according to Applicant "is located within an exon of the integrin B1 gene". This disclosure does not provide explicit support for an artificial intron that contain sequence that specifically targets an exon of any target gene, as instantly claimed.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 7, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Cheo et al. (US Patent No. 7,393,632).

The instant claims are drawn to an isolated RNA comprising an artificial intron RNA that is released in a cell thereby modulating the function of a target gene wherein the cell is a mammalian or a eukaryotic cell and drawn to a cultivated cell and a composition comprising said isolated RNA.

Cheo et al. teach isolated RNA molecules comprising sequences that can be released in a cell wherein the sequences are capable of interfering with the expression of a target gene. Cheo et al. teach said sequences can be intron like sequences flanked by intron/exon sites wherein the sequences can be antisense RNA, ribozyme or dsRNA capable of RNAi (see at least column 112) and teach these sequences can be in eukaryotic cells (see cat least column 89). Cheo et al. teach isolated RNA transcripts that contain splice donor sites, splice acceptor sites, branch sites and pyrimidine tract sequences that allow splicing in vivo in cells (see Examples 13 and 14).

Thus, Cheo et al. anticipates claims 1, 2, 3, 7, 11 and 12 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 11, 19 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo et al. (US Patent No. 7,393,632), Mitchell et al. (of record cited on form 892 mailed 03/11/2008), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54 of

record PTO Form 892 mailed 03/11/2008), Zhuang et al. (PNAS Vol. 86: 2752-2756 of record PTO Form 892 mailed 03/11/2008, Coolidge et al. (of record cited on 892 mailed 01/23/2009) and Bennett et al. (US Patent No. 6,710,174).

The instant claims are drawn to an isolated RNA comprising an artificial intron RNA that is released in a cell thereby modulating the function of a target gene wherein the cell is a mammalian or a eukaryotic cell and drawn to a cultivated cell and a composition comprising said isolated RNA, wherein the isolated RNA contains a polypyrimidine tract having SEQ ID No. 2, contains a donor site as recited in claim 4, contains an acceptor site as recited in claim 5, a branch site as recited in claim 6 and a polypyrimidine tract that includes SEQ ID No. 2.

Cheo et al. is relied upon as above. Cheo et al. do not teach a splice donor and acceptor sites, branch sites and polypyrimidine sequences containing the claimed sequences as recited in the claims and do not teach the RNA targets an exon of a target gene.

Mitchell teach an efficient splice acceptor site having the sequence of CCACAGC (see column 12, lines 15-20) that is capable of efficiently splicing pre-mRNA along with branch sites, donor sites and polypyrimidine tract sequences.

Krawczak et al. teach a 5' splice donor site having a sequence that contains AAGTAAGT (see page 41).

Zhuang et al. teach a preferred branch site sequence for mammalian mRNA splicing having the sequence UACUAAC (see page 2752).

Coolidge et al. teach the polypyrimidine tract is essential in pre-mRNA splicing and teach the sequence of the polypyrmidine tract is flexible but for efficient splicing, the tract must contain a threshold of 8 uridine residues (see pages 888-889).

Bennett et al. teach exon regions are preferred target sites for inhibitory nucleic acid molecules (see at least column 7).

It would have been obvious to incorporate the acceptor site taught by Mitchell, the 5' donor splice site taught by Krawczak et al. and the branch site sequence taught by Zhuang et al. into the DNA template or isolated RNA comprising an intron RNA taught by Mitchell. It would have been further obvious to incorporate a polypyrmidine tract as claimed.

One of skill in the art would have been motivated to incorporate the acceptor site taught by Mitchell as it is shown this site efficiently allow proper splicing of therapeutic pre-mRNA sequence and one would have wanted to use the 5' donor splice site because Krawczak et al. teach the efficiency of splicing is critically dependent upon the accuracy of cleavage and rejoining and given this splice donor sequence has been identified as a consensus sequence for splicing, one would have wanted to use the most effective sequence to allow accurate splicing activity in cells to release the sequence as taught by Cheo et al. One of skill in the art would have been further motivated to use the branch site sequence taught by Zhuang et al. because Zhuang et al. demonstrated that this sequence is preferred in mammalian cells for accurate splicing of mRNA sequence. Given Coolidge et al. teach the sequence of the polypyrimidine tract is flexible but must contain at least a threshold of eight uridines, it

would have been a matter of routine experimentation to the skilled artisan to construct and test polypyrmidine tracts that would contain the claimed sequence and incorporate the optimal sequence into the claimed RNA. Moreover, it is well known in the art that exon regions are preferred target sites for inhibitory nucleic acid molecules such as antisense compounds as taught by Bennett et al. and it would have been obvious to target said region.

Finally, one would have expected to be able to incorporate the sequences taught by Mitchell et al., Krawczak et al. and Zhuang et al. into the DNA template for the isolated RNA given both demonstrate that each sequence is capable of mRNA splicing and further teach said sequence is the preferred sequence for accurate splicing of mRNA in cells. One would have expected to be able to make and find the optimal polypyrimidine tract because Coolidge et al. teach how to make the optimal composition.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Argument

Claim Rejections - 35 USC § 102 - withdrawn

The rejection of claims 1, 3, 7, 11 and 19 under 35 U.S.C. 102(e) as being anticipated by Beach et al. (US 20030084471) is withdrawn.

Claim Rejections - 35 USC § 103 - withdrawn

The rejection of claims 1-8, 11, 19 and 58-60 under 35 U.S.C. 103(a) as being unpatentable over Beach et al. (US 20030084471), Mitchell et al. (of record cited on form 892 mailed 03/11/2008), Krawczak et al. (Hum Genet 1992, Vol. 90: 41-54 of record PTO Form 892 mailed 03/11/2008), Zhuang et al. (PNAS Vol. 86: 2752-2756 of record PTO Form 892 mailed 03/11/2008, Coolidge et al. (of record cited on 892 mailed 01/23/2009) is withdrawn..

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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